



Caudal Neostigmine and Clonidine as Adjuncts to Bupivacaine for Post Operative Analgesia in Children Undergoing Sub Umbilical Surgery

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Abstract

Background: Caudal block has evolved to become the most popular regional anesthetic technique for use in children. It provides excellent analgesia during surgery as well as during postoperative period in subumbilical surgeries in children, however one of the major limitations of the single injection is relative short duration of post operative analgesia even with long acting local anesthetics such as Bupivacaine. This problem can be circumvented by the use of different adjunct drugs to the local anesthetic solutions. The aim of the present study was to compare the analgesic efficacy and safety of Neostigmine - bupivacaine mixture to that of bupivacaine- clonidine mixture following caudal administration in children undergoing infra-umbilical surgeries.

Methods: In a prospective, randomized, double blind study, 100 patients of ASA physical status I of either sex in the age range of 1 to 5 years scheduled for elective infra-umbilical surgical procedures were randomly allocated to one of the groups of 50 patients each to receive caudal injection of either 1µg/Kg of clonidine in addition to 1ml/kg of 0.25% bupivacaine hydrochloride in Group BC or 2µg/Kg of neostigmine added to 1ml/kg of 0.25% bupivacaine hydrochloride in Group BN. The perioperative hemodynamic effects, post operative pain scores (OPS), supplementary analgesic requirement and side effects were assessed by a blind observer during 24 hour observation period.

Results: Both the groups were homogenous with reference to age, sex, weight and duration of anesthesia and duration of surgery. No significant differences with respect to mean heart rate, blood pressure (systolic and diastolic) and oxygen saturation were noted during perioperative period between the two groups. The mean duration of analgesia in group BC was 10.87±3.5 hours while in group BN mean duration of analgesia was 4.26±1.6 hours. The duration of analgesia in group BC was longer and the difference was statistically significant ($p < 0.05$). In the postoperative period rescue analgesia in the form of diclofenac suppository (1mg/kg) was required in 16 patients (32%) in the group BC and 31 (62%) patients in the group BN. Statistically a significant difference ($p < 0.001$) was observed between the two groups. In our study 2 patients in BC (group) had nausea and vomiting (4%), while in group BN 3 patients had nausea and vomiting (6%). The total number of patients who had side effects was less in study group compared to control group. However, the difference was statistically insignificant ($p > 0.05$) between the two groups.

None of our patient developed any other complication. In our study there was very low incidence of nausea and vomiting which was probably due to i/v ondansetron given intra operatively.

Conclusion: Caudal clonidine provides effective and prolonged intra and postoperative analgesia in patients undergoing infra-umbilical surgeries. Neostigmine and clonidine when added to caudal bupivacaine are safe and without any significant side effects.

Keywords: caudal anesthesia, neostigmine, clonidine, post operative pain, children, bupivacaine.

INTRODUCTION

Caudal epidural block is one of the most common regional anesthetic techniques used in children. It is generally considered a simple and safe procedure but its main disadvantage is its relatively short duration of action, even with the use of long-acting local anesthetic agents such as bupivacaine.¹ In order to improve the duration of action and quality of analgesia of a caudal block with bupivacaine, various drugs have been used, e.g. opioids, epinephrine, midazolam, neostigmine, ketamine and clonidine.²

Since the discovery that epidural clonidine, an alpha 2 receptor agonist, produces analgesia, the drug has been used increasingly in anesthetic practice.^{3,4} Clonidine has been shown to produce analgesia without causing significant respiratory depression after systemic, epidural or spinal administration. Although epidural clonidine may also cause hypotension, bradycardia and sedation in higher doses, serious adverse effects are uncommon in the dose range (1-2 µg/kg body weight) normally used in children.⁵

Neostigmine, like all cholinesterase inhibitors, causes analgesia by preventing the breakdown of acetylcholine in the spinal cord; its use in post-operative analgesia was described as early as the 1990s, both in adults and in children.^{6,7,8} Acetylcholine has been shown to induce analgesia by increasing cyclic GMP by generating nitric oxide.⁹

The present study was carried out to evaluate the analgesic efficacy of clonidine and neostigmine as adjuncts to caudal bupivacaine for post operative pain relief in children.

MATERIALS AND METHODS

This prospective, randomized and double blinded study entitled "Neostigmine and clonidine as

adjuncts to Bupivacaine, for caudal block in children undergoing infra-umbilical surgeries" was conducted in the Department of Anesthesiology and Critical Care at Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir from June 2014 to May 2016. After taking Institutional Review Board approval, 100 patients belonging to ASA physical status I, in the age range of 1- 5 years of either sex, for infra-umbilical surgeries were recruited for the study. The sample size was divided into two groups BC and BN, having 50 patients each. caudal injection of either 1µg/Kg of clonidine in addition to 1ml/kg of 0.25% bupivacaine hydrochloride in Group BC or 2µg/Kg of neostigmine added to 1ml/kg of 0.25% bupivacaine hydrochloride in Group BN was done. Patients allergic to local anesthetic, Spinal deformity, Neurological disease, Coagulopathy, Bleeding diathesis and Infection near the site of injection were excluded from the study.

The sterile syringes containing equal volumes of content, one containing bupivacaine and clonidine and other containing bupivacaine and neostigmine were loaded by the anaesthesiologist not participating in the study. The intraoperative monitoring and postoperative observation were done by the anaesthesiologist who administered the drugs, but were unaware of the contents.

All the patients underwent thorough pre-anaesthetic checkup pre-operatively, and a written consent was taken from the parents/ guardians, explaining all risks and benefits. In the operation room baseline monitoring like heart rate (HR), non- invasive blood pressure (NIBP), ECG and pulse oxymetry (SpO₂) were recorded. After securing IV access with 22G iv cannula patients were induced with inj. Propofol (1-2mg/kg) and inj. Atracurium (0.5mg/kg). Airway was secured

with appropriate size endotracheal tube. Maintenance was done with O₂ (33%) + N₂O(67%) + isoflurane 0.6% to 1% and supplementary doses of atracurium. Injection ondansetron 0.1mg/kg i/v was given intraoperatively 30 minutes before the expected extubation. Patients were positioned in lateral position for caudal block. Under all aseptic precautions, caudal block was performed by using 22/24G needle with bevel, using loss of resistance technique to saline. After proper identification of caudal space, drug was injected and antiseptic dressing was applied. The duration of analgesia was taken as from onset of caudal block to time of first dose of rescue analgesia. In the intra operative period the degree of analgesia was analyzed by objective assessment of vitals including heart rate, blood pressure. The parameters were recorded at the following intervals: baseline, before incision, immediately after surgical incision and then every 5 minutes till the end of surgery.

Postoperatively patients were assessed at 0 minutes, 30 minutes, 60 minutes, 4, 8, 12 and 24hrs by using FLACC Pain scale. FLACC (Face, Legs, Activity, Cry, console ability) pain scale consists of five parameters, each given a score of 0-2. Total score is taken to assess the pain. Score "0" No pain, "1-3" Mild pain, "4-7" Moderate pain, "8-10" Severe pain

Rescue analgesia, diclofenac suppository (1mg/kg) was given if pain score was ≥ 4 . The time of first rescue analgesia administration and number of doses of rescue medication was noted in both groups. An increase in heart rate within 15 minutes of skin incision more than 15% indicated failure of caudal analgesia and rescue analgesia was given.

The data was collected from both the groups, and compared for duration and degree of analgesia, complications and need for rescue analgesia.

The data thus obtained was analyzed statistically using students 't' test. A 'p' value of < 0.05 was considered statistically significant.

The FLACC Pain Scale

Categories	Scoring		
	0	1	2
Face	Smile or no particular expression	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consol ability	Content, relaxed	Reassured by occasional touching, hugging or talking to, distractable	Difficult to console

RESULTS AND OBSERVATIONS

The study was conducted over a 2 years period (June 2014 to May 2016). Demographic patterns

and preoperative vital parameters were similar when the two groups were compared [Table 1].

Parameters	Group BC (n=50)	Group BN (n=50)	P value
Age (years)	3.5 ± 1.13	3.45 ± 1.1	0.96
Weight (kg)	21.6 ± 3.2	19.0 ± 4.2	0.61
Preoperative pulse (bpm)	100.50 ± 7.5	101.28 ± 5.0	0.5
Preoperative SBP (mmHg)	96.54 ± 4.8	97.4 ± 5.6	0.43
Preoperative DBP (mmHg)	56.6 ± 4.3	56.3 ± 4.2	0.62
Preoperative SpO ₂ (%)	98.66	98.64	0.13

Data are given as mean±SD. Test done: Independent sample *t* test, \$Pearson Chi square. *n*: Number of patient; bpm: Beats per minute; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SpO₂% : oxygen saturation by pulse oxymetry

Heart rate, oxygen saturation by pulse oxymetry (SpO₂%), systolic blood pressure and diastolic blood pressure were recorded at 5 minutes of intervals intraoperatively starting from baseline, before skin incision, immediately after incision,

then every 5 minutes till the end of surgery. The mean heart rate was (95.6±1.4) in BC group and (96.7±0.4) in BN group. The mean of systolic BP was (94.8±1.5) in BC group and (95.7±0.5) in BN group. The mean DBP was (54.4±3.4) in BC group and (54.73±5.4) in BN group. The groups were compared with reference to mean heart rate, mean oxygen saturation, mean systolic blood pressure and mean diastolic blood pressure intraoperatively and the difference was found to be statistically insignificant ($p>0.05$) [Table 2].

Parameter	Group BC (n=50)	Group BN (n=50)	P value
Overall Mean Heart Rate±SD	95.6±1.4	96.7±0.4	0.2
Overall Mean SBP ± SD	94.8±1.5	95.7±0.5	0.21
Overall Mean DBP ± SD	54.4±3.4	54.73±5.4	0.65
Overall Mean SPO2 ± SD	98.48	98.38	0.5

Quality of postoperative analgesia in PACU was assessed by using FLACC pain scale at 0 minute, 30minutes and 60minutes. A statistically significant difference ($p<0.001$) was observed in FLACC pain scores between the two groups at 0minute, 30minutes and 60minutes. Mean scores at 0 minutes, 30 minutes and 60 minutes in BC group were 1.53±1.6, 1.86±0.7and 2.38±0.58 respectively. Mean scores at 0minutes, 30minutes and 60 minutes in BN group were 1.90±0.5, 2.06±0.5 and 2.62±0.6 respectively. Quality of postoperative analgesia in ward was assessed by

using FLACC scale at different time intervals, i.e; 4hr, (after the discharge from PACU) 8hr, 12hr and 24hr. Mean scores at 4hr,8hr,12hr,24hr in BC group were 2.54±0.522, 3.00±0.4, 3.27±0.494 & 3.63±0.89 hrs respectively. Mean scores at 4hr, 8hr, 12hr, 24hr in BN group were 3.38±0.55, 4.16±0.9, 4.71±1.538 & 5.42±2.052 hrs respectively. There was a statistically significant difference in FLACC scores at various intervals between the two groups, FLACC scores being less in BC group compared to BN group ($p<0.001$) [Table 3].

Time(min)	Group BC (n=50)	Group BN (n=50)	P Value
0 min	1.53±1.6	1.90±0.5	0.04
30min	1.86±0.7	2.06±0.5	0.032
60min	2.38±0.58	2.62±0.6	0.013
4hrs	2.54±0.522	3.38±0.55	<0.01
8hrs	3.00±0.4	4.16±0.9	<0.01
12hrs	3.27±0.494	4.71±1.538	<0.01
24hrs	3.63±0.89	5.42±2.052	<0.01

In the postoperative period rescue analgesia in the form of diclofenac suppository (1mg/kg) was required in 15 patients (30%) in the BC group and 31 (62%) patients in the BN group. Statistically a significant difference ($p<0.001$) was observed

between the two groups. In our study the mean time to first rescue analgesia was 10.87±3.5 hours in the BC group while it was 4.26±1.6 hours in BN group. Statistically a significant difference ($p<0.001$) was observed. In our study 3 patients in

BN (group) had nausea and vomiting (6%), while in BC group 2 patients had nausea and vomiting (4%). The total number of patients who had side effects were less in BC group compared to BN group. However, the difference was statistically insignificant ($p>0.05$) between the two groups.

None of our patient developed any other complication In our study there was very low incidence of nausea and vomiting which was probably due to i/v ondansetron given intra operatively {TABLE 4}.

Parameters	Group BC (n=50)	Group BN (n=50)	P Value
First dose of rescue analgesia(hours)	10.87±3.5	4.26±1.6	0.001
Number of doses of rescue analgesia	5.34±1.6	8.47±1.3	<0.001
Total number of patients receiving rescue analgesia	15 (30%)	31 (62%)	
Patients with side effects	2(4%)	3(6%)	0.685
Patients with no side effects	48	47	

Data are given as mean±SD. n: Number of patient, Test done: Independent sample t test. *Statistically significant; bpm: Beats per minute; mins: Minutes

DISCUSSION

Most commonly used procedure to treat pain in children is caudal block. It is simple, safe and effective. It can be used with or without additives. Additives are used to prolong duration of analgesia postoperatively.

This study was carried out to compare the quality and duration of analgesia of caudal bupivacaine with adjuncts neostigmine and clonidine. Two groups of 50 patients each were randomly selected for this study. The data collected and analyzed statistically was age, body weight, hemodynamic parameters (heart rate, systolic BP and Diastolic BP) and oxygen saturation by pulse oxymetry (SpO₂%), quality of analgesia by using FLACC pain scores, rescue analgesia, time of first Rescue analgesia (Duration of analgesia) and postoperative complications.

Age and weight were comparable in both the group ($P>0.05$). All the caudal blocks were taken as successful. we were unable to detect any significant hemodynamic differences between our groups of patients. No patient required drug therapy to treat hypotension or bradycardia. No episode of oxygen saturation < 95% was recorded. Our observations correlate with Klimsha et al(1998) who found no significant hemodynamic effects in their patients receiving either 1 or 2µg/kg of caudal clonidine.¹⁰ Wanda joshi et al (2004) were also unable to observe hemodynamic

differences between two groups of patients who received caudal bupivacaine (0.125%) with an equal volume of either clonidine (2µg/kg) or saline.¹¹ Jamali et al.(1994) only studied baseline mean arterial pressure(MAP) and at 3 hours after procedure. No differences in MAP were seen with the administration of 1µg/kg of caudal clonidine.¹² Contrarily Syedhijazi M et al(2008) observed that heart rate, systolic and diastolic blood pressure were significantly lower in clonidine group than in bupivacaine group.¹³

The pain scores were assessed by FLACC scale postoperatively in PACU and ward. BC group was having less pain scores as compared to BN group. The difference was statistically significant ($p<0.05$). During the last decade the use of clonidine has become increasingly popular in pediatric anesthesia, particularly when administered caudally with a local anesthetic agent.¹⁴ The addition of clonidine as an adjuvant has allowed the use of lower concentration of the local anesthetic for achieving the same level of analgesia which increases the margin of safety and reduces the incidence of unwanted motor blockade (Tsui BC, Berde CB 2005; Hansen TG, Henneberg SW, Walther Larsen S 2004).¹⁵ Turan A et al (2003) in their study “Caudal Ropivacaine and Neostigmine in Pediatric Surgery” studied the comparison of the addition of

neostigmine on duration of caudal block produced by 0.2% ropivacaine 0.5ml/kg in control group and 0.2% ropivacaine 0.5ml/kg plus 2mcg/kg neostigmine in study group. They found that there was no difference between the group members in heart rate, mean arterial pressure and spo2 during the study. Severe bradycardia or hypotension was not observed in any patient. The pain scores were significantly lower in group II (study) when compared with group I (control), 7 (31%) children in study group and 18(81%) children in control required rescue analgesia during first 24hrs period. Which was statistically significant ($p<0.05$).¹⁶ Our observation correlate with that of Motsch J et al (1997), Children given a combined administration of caudal clonidine and bupivacaine resulted in significantly better and longer post operative analgesia when compared to bupivacaine alone. This was confirmed by longer time of interval to first request of analgesic and by lower number of analgesic requests.¹⁷ Lee JJ and Rubin AP (1944) also observed that caudal analgesia in children with clonidine - bupivacaine combination resulted in longer duration of post operative analgesia and reduced frequency of parental opioid administration.¹⁸ Yildiz T.S (2006) et al. also observed that children undergoing elective inguinal repair receiving caudal clonidine – bupivacaine combination had increased duration of post operative analgesia without any respiratory and hemodynamic side effects.¹⁹

The total number of patients who required rescue analgesia (diclofenac suppository) in post-operative period were less from study group as compared to control group and the difference was statistically significant ($p<0.05$). Comparison showed that adding clonidine with bupivacaine decreased the overall requirement of rescue analgesia postoperatively. The mean time to first rescue analgesia in BC group was more than BN group. Emil Batarseh MD et al (2015), in their study “Caudal Bupivacaine–Neostigmine Effect on Post-operative Pain Relief in children” administered caudal bupivacaine 0.25% 0.5ml/kg (group I), bupivacaine 0.25% 0.5ml/kg plus

1.5mcg/kg neostigmine (group II), bupivacaine 0.25% 0.5ml/kg plus 3mcg/kg neostigmine (group III) and bupivacaine 0.25% 0.5ml/kg plus 6mcg/kg neostigmine (group III). They found that significantly more patients of plain bupivacaine group received postoperative rescue analgesics than Bupivacaine –Neostigmine groups.²⁰ Mohamed Abdulatif et al (2002), in their study “Caudal Neostigmine, Bupivacaine, and Their Combination for Postoperative Pain Management After Hypospadias Surgery in Children” found that caudal administration of bupivacaine with the addition of neostigmine resulted in superior analgesia as compared with other two groups. Time to first rescue analgesia was 22.8 ± 2.9 hrs, 8.1 ± 5.9 hrs and 5.2 ± 2.1 hrs in the bupivacaine/neostigmine, bupivacaine, and neostigmine groups respectively ($p<0.01$).²¹ Dr Rudra et al (2005), in their study “scope of caudal neostigmine with bupivacaine for post-operative analgesia in children: comparison with bupivacaine” studied the comparison of the addition of neostigmine on duration of caudal block produced by 0.25% bupivacaine 1ml/kg and 0.25% bupivacaine 1ml/kg plus 2mcg/kg neostigmine. They found that the mean time to first rescue analgesia was 7.6 ± 5.4 hours in the study group while it was 19.0 ± 4.2 hours in control group. Statistically a significant difference ($p<0.001$) was observed in both the groups.²²

In our study 3 patients in BN (group) had nausea and vomiting (6%), while in BC group 2 patients had nausea and vomiting (4%). The total number of patients who had side effects were less in BC group compared to BN group. However, the difference was statistically insignificant ($p>0.05$) between the two groups. None of our patient developed any other complication. In our study there was very low incidence of nausea and vomiting (10%) which was probably due to i/v ondansetron given intraperatively. Dr Pramod Gupta et al (2011), found that there were no incidence of nausea vomiting in their study. “Neostigmine as an adjunct to Bupivacaine, for caudal block in burned children, undergoing skin

grafting of the lower extremities” in which they used 0.125% & 0.25% bupivacaine, along with fixed dose of neostigmine (6mcg/kg). The results were due to preoperative i/v ondansetron administration.²³ Motsch J et al.(1997) observed low incidence of vomiting in clonidine – bupivacaine group as compared to bupivacaine alone.²⁴ Naguib et al (1991) observed patients having nausea/ vomiting, urinary retention ,muscle weakness in post operative period after caudal bupivacaine and ketamine.²⁵

From the result of this study we conclude the clonidine when added to caudal bupivacaine provided superior quality and longer duration of analgesia requiring less doses of rescue analgesia in post operative period compared to bupivacaine with neostigmine at no additional risk.

CONCLUSION

Thus we concluded that clonidine as an adjunct to caudal block with bupivacaine significantly increases the intensity and duration of postoperative analgesia in pediatric patients undergoing infra-umbilical surgeries.

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